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Reorganization of Sensory Modalities Evoked by Microstimulation in Region of the Thalamic Principal Sensory Nucleus in Patients With Pain Due to Nervous System Injury

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ABSTRACT

Stimulation of the somatosensory system is more likely to evoke pain in patients with chronic pain after nervous system injury than in patients without somatosensory abnormalities. We now describe results of stimulation through a microelectrode at microampere thresholds (threshold microstimulation; TMIS) in the region of the human thalamic principal sensory nucleus (ventral caudal; Vc) during operations for treatment of movement disorders or of chronic pain. Patients were trained preoperatively to use a standard questionnaire to describe the location (projected field) and quality of sensations evoked by TMIS intraoperatively. The region of Vc was divided on the basis of projected fields into areas representing the part of the body where the patients experienced chronic pain (pain affected) or did not experience chronic pain (pain unaffected) and into a control area located in the thalamus of patients with movement disorders and no experience of chronic pain. The region of the Vc was also divided into a core region and a posterior-inferior region. The core was defined as the region above a standard radiologic horizontal line (anterior commissure-posterior commisure line; ACPC line) where the majority of cells responded to innocuous somatosensory stimulation. The posterior-inferior area was a cellular area posterior and inferior to the core.

In both the core and the posterior-inferior regions, the proportion of sites where TMIS evoked pain was larger in pain-affected and unaffected areas than in control areas. The number of sites where thermal (warm or cold) sensations were evoked was correspondingly smaller, so that the total of pain-plus-thermal (sensation of warmth or cold) sites was the same in all areas. Therefore, sites pain where stimulation evoked pain in patients with neuropathic pain (i.e., pain following an injury to the nervous system) may correspond to sites where thermal sensations were evoked by stimulation in patients without somatosensory abnormality. J. Comp. Neurol. 399:125–138, 1998. © 1998 Wiley-Liss, Inc.

Indexing terms: human thalamic ventral posterior nucleus; spinothalamic tract; somatosensory plasticity; nervous system injury

The region of the human thalamic principal sensory nucleus (ventral caudal; Vc) can be mapped by neuronal receptive fields (RFs) to somatosensory stimulation (Poggio and Mountcastle, 1963; Jones et al., 1982; Kaas et al., 1984; Lenz et al., 1988a) or by the locations of sensations (projected fields; PFs) evoked by microstimulation (Lenz et al., 1993a). Maps based on the spatial organization of RFs are referred to as RF maps, whereas those based on PFs are referred to as PF maps. Reorganization of thalamic RF maps following injuries of the nervous system is well established (Lombard et al., 1979; Pollin and Albe-

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Fessard, 1979; Albe-Fessard and Lombard, 1983; Lenz et al., 1987, 1988a–c, 1994a–c, 1998a,b; Garraghty and Kaas, 1991; Rasmusson, 1996a,b). RF maps identify the reorganization of inputs to the thalamus that occurs following injury. In contrast, alterations in sensations evoked by stimulation of the thalamus may identify reorganization of the image of the body embedded in the thalamus or cortex (Lenz et al., 1987, 1994c, 1998). It has been reported that pain is evoked more frequently by stimulation in the region of Vc in patients with neuropathic pain (i.e., pain following an injury to the nervous system) than in patients without such pain (Levin, 1966; Obrador and Dierssen, 1966; Dierssen et al., 1969; Mazars et al., 1974; Lenz et al., 1988c; Davis et al., 1996). However, the results of stimulation have not been studied systematically by using a standardized protocol for measuring sensation.

We now report sensations evoked by stimulation of the region of the Vc at microampere current levels (threshold microstimulation; TMIS; Lenz et al., 1993a). TMIS-evoked sensations were described by using a validated questionnaire and protocol (Lenz et al., 1993a, 1994a, 1995a, 1997). The same questionnaire was used to describe cutaneous stimuli applied during preoperative sensory testing. Therefore, the sensations evoked by intraoperative TMIS were measured in the context of sensations evoked by natural cutaneous stimuli. This technique has now been applied to the region of Vc in patients undergoing thalamic stereotactic procedures for neuropathic pain. Results in these patients were compared with those in "control" patients undergoing surgery for the treatment of movement disorders. The results of this study suggest that thalamic sites signaling thermal modalities in control areas may have been transformed to signal pain in patients with chronic pain.

MATERIALS AND METHODS

These studies were carried out at the Johns Hopkins Hospital during the physiologic exploration of the thalamus that preceded thalamotomy for treatment of movement disorders or implantation of deep brain-stimulating electrodes for the treatment of chronic pain. The protocol used in these studies conformed to the principles stated in the Declaration of Helsinki regarding the use of human subjects and was reviewed and approved annually by the Joint Committee on Clinical Investigation of the Johns Hopkins University. All patients signed an informed consent.

The core of Vc was defined as the cellular region where the majority of cells responded to innocuous somatosensory stimulation (Lenz et al., 1988b, 1993a, 1994a) and was identified in each patient studied (see Figs. 2–4). The posterior-inferior region was defined as the cellular region posterior and inferior to the core where somatic sensations were evoked by TMIS. Sensations were evoked by stimulation at sites up to 5 mm posterior to the border of the core (Lenz et al., 1993a, 1994c, 1998) in the posterior-inferior area. In patients with chronic pain, the location of the PF was used to classify the region of Vc into areas (PF areas) representing the painful (pain-affected) and nonpainful (pain-unaffected) parts of the body. In patients with movement disorders, the region of Vc was referred to as the control area. PFs crossing the border of the painful area were included in the pain-affected areas, and the description of the sensation in the painful area was used. In this protocol, sites where TMIS evoked no response could not be classified as pain affected or unaffected and were excluded from the analysis.

Somatosensory testing protocols

All patients underwent at least one session of preoperative sensory testing for training in the use of a questionnaire for describing somatic sensation (see Fig. 1) and to identify abnormal somatosensory function. During sensory testing of patients with movement disorders, sites on the face, arm, and leg were stimulated with a battery of stimuli, including a camel hair brush, a brass probe (2 cm diameter) at room temperature, a brass probe at 0°C, a tuning fork (128 Hz), and a 3-inch stainless-steel straight edge. Von Frey hairs were used to determine pain and detection thresholds for mechanical stimuli. Thermal stimuli included a 5-second application of the black delrin and brass probes at room temperature as well as brass probes that were heated to temperatures of between 40°C and 53°C or cooled to 0°C. Stimulation by the room-temperature probe was inserted randomly into the series of thermal stimuli to assess response accuracy. Approximate temperature thresholds for detection of innocuous warmth and for pain produced by heat were determined by using an ascending-staircase method with these probes (Gracely et al., 1978). Testing included the part of the body where the patient experienced chronic pain and abnormal somatosensory function as well as parts of the body where pain or sensory abnormalities were not observed.

With application of each stimulus, the patient described the sensation by using the questionnaire shown in Figure 1. The patient was asked to decide whether the sensation was natural by identifying the stimulus and judging whether the stimulus was "something that you might encounter in everyday life." Neither question 1 nor question 2 was a forced choice. If the sensation was nonpainful, then the patient chose from the left list, which was labeled nonpainful. If the sensation was painful, then the patient chose from the right list, which was labeled painful. Under question 4, the patient was asked to identify which of the four classes of sensation applied (mechanical, movement, temperature, tingle) and then to identify a descriptor or descriptors within the chosen class.

Abbreviations

AC	anterior commissure
MG	medial geniculate nucleus
NR	no response
PC	posterior commissure
PF	projected field
RF	receptive field
Vc	human ventral caudal thalamic (principal somatosensory) nucleus (corresponding to monkey ventral posterior nucleus, which is composed of a lateral division that represents the body and a medial division that represents cranial structures)
Vcpc	ventral caudal parvocellular nucleus (corresponding to monkey ventral posterior-inferior nucleus)
Vcpor	ventral caudal portae nuclei(monkey pulvinar oral; posterior and inferior subnuclei of Vc, respectively)
Vim	human ventral intermediate thalamic (cerebellar relay) nucleus (corresponding to monkey ventral posterior lateral oral nucleus)
Vmpo	primate thalamic nucleus ventral medial posterior
Voa	ventral oral anterior nucleus
Vop	human ventral oral posterior thalamic (pallidal relay) nucleus (corresponding to monkey ventral lateral oral nucleus; Hirai and Jones, 1989)

Which words describe the sensation that you feel?

1) Totally Natural/ Almost Natural/ Possibly Natural/ Rather Unnatural/ Totally Unnatural
2) Clearly on the skin surface/ Definitely below the skin surface/ Both
3) Painful/ Non-painful
4) Quality of sensation:

Non-painful	Painful
Mechanical	Mechanical
Touch	Drilling
Pressure	Stabbing
Sharp	Sharp
Movement	Squeezing
Vibration	Tugging
Movement	Tearing
Temperature	Dull
Warm	Splitting
Cool	Temperature
Tingle	Hot
Electric current	Burning
Tickle/ itch	Cold
	Movement
	Spreading
	Flashing
	Flickering
	Throbbing
	Tingle
	Itching
	Electric Current
	Emotion
	Frightful
	Nauseating
	Cruel
	Suffocating
	Fatiguing

5) Rate this sensation with respect to your pain.

Identical/ Almost Identical/ Possibly Identical/ Rather Different/ Totally Different

Fig. 1. The questionnaire used to describe sensations evoked by thalamic threshold microstimulation (TMIS). The patient was asked to choose "which words describe the sensation that you feel." See text.

Patients were allowed to specify the class (e.g., tingle) as a descriptor if the descriptors within that class were not applicable. After choosing a descriptor in one class, the patient was asked whether the other three classes might apply to a component of the sensation. Patients were allowed to specify descriptors that were not included in the questionnaire.

Intraoperative procedures

Physiologic exploration of the thalamus was carried out under local anesthetic, as described previously (Lenz et al., 1988a,b, 1993a). Briefly, the stereotactic coordinates of the anterior commissure (AC) and posterior commissure (PC) were determined by using computer-assisted tomography. These coordinates were used to generate maps of the human thalamus in sagittal section. These maps were transformations of the standard atlas map (Schaltenbrand and Bailey, 1959) that matched the anterior commissure-posterior commissure (ACPC) line in each patient (Hawrylyshyn et al., 1976).

The stereotactic target was confirmed physiologically by recording the activity of single neurons and stimulating

with the use of a microelectrode (impedance 1.5–3.0 mega-Ohms; Lenz et al., 1988a). Trajectories were directed toward the Vc through a coronal burr hole and, thus, passed through the Vc from anterior dorsal to posterior ventral (see Fig. 2). The first trajectory targeted the Vc, because the response of cells in this area to somatosensory stimulation was the most reliable physiologic landmark with which to guide the operation (Lenz et al., 1995b).

Sites were explored starting 1 cm above the target and were characterized by the location of the sensation evoked (PF) by threshold stimulation of the thalamus at microampere current levels (TMIS). Sites where isolated, single neurons could be recorded were characterized by spontaneous activity (Lenz et al., 1989, 1994c, 1988c; Zirh et al., 1997) and by the neuronal response to innocuous somatosensory stimuli (Lenz et al., 1988b). The activity of isolated, single neurons was studied in response to stimuli, including light touch, tapping or pressure to skin, deep pressure to muscles or ligaments, and passive joint movement. Cells responding to stimulation of the skin were classified as cutaneous cells. Cells responding to stimulation of deep structures (joints, ligaments, etc.) but not to stimulation of skin deformed by these stimuli were classified as deep cells. A reproducible response to repeated application of a stimulus in one part of the body was required to identify a neuronal receptive field. Innocuous thermal stimuli (sensation of warmth or cold) and noxious heat/mechanical stimuli were applied within the RF and PF at many of the sites where TMIS was carried out (Lenz et al., 1993b, 1994b; Lenz and Dougherty, 1998). The signal from a foot switch was used to indicate the timing of peripheral stimuli. During surgery, a tape recording was made of the microelectrode signal, the signal from the foot switch, a verbal description of stimulation procedures, instructions to the patient, and additional comments.

Microstimulation was delivered in trains of approximately 1-second duration at 300 Hz by using a biphasic pulse consisting of a 0.2 msec anodal pulse followed in 0.1 msec by a cathodal pulse of the same duration and magnitude. Stimulation was initially carried out at 40 μA at sites located 1 mm apart along the trajectory. When a sensory response was evoked, stimulation was subsequently carried out once along every 0.5 mm on the trajectory. At each stimulation site, patients were first asked whether they felt anything. If a sensation was evoked, then a threshold was established; if no sensation was evoked at 40 μA, then no response (NR) was indicated at that site. The threshold was established by lowering the current for successive stimuli until a sensation was no longer evoked. The current was then increased until a sensation was again evoked. This procedure often was repeated once to verify the threshold.

Once a threshold had been established, the patient was questioned to determine the location of the sensation evoked by stimulation (PF). Thereafter, the same questionnaire that was used during preoperative sensory testing was administered, so that the patient could describe the nature of the TMIS-evoked sensation. TMIS was repeated several times to determine the location of the PF and to complete the questionnaire. This protocol was followed at each stimulation site, so that data are reported in terms of results at individual stimulation sites, including sites where no sensation was evoked.

RESULTS

Results of stimulation were studied in ten patients with movement disorders, including Parkinsonian tremor (n = 4), essential tremor (n = 4), and cerebellar tremor (n = 2). Patients with pain (n = 12) were diagnosed as having poststroke central pain syndrome (PSP; n = 4), spinal cord injury central pain syndrome (n = 4; Lenz et al., 1994c), and pain following peripheral nervous system injury (n = 4), including two amputees with stump pain (Lenz et al., 1998). All patients with pain had a history of nervous system injury and evidence of sensory loss in the region of their ongoing pain. All had failed treatment with antidepressants in therapeutic doses and with anticonvulsants and opiates. In these 22 patients, sensations were evoked by stimulation at 384 sites in the region of the Vc. Warm sensations were evoked by stimulation at 10% (37/384) of sites, cold was evoked at 3% (12/384) of sites, pain was evoked at 8% (32/384) of sites, and paresthesia was evoked at 79% (303/384) of sites. There were 43 sites where no response (NR) was evoked by stimulation in the region of Vc. NR stimulation sites tended to be less common($P > 0.25$; χ^2 test) in patients with movement disorders (8%; 12/151) than in patients with chronic pain (11%; 31/277).

Results in a patient with Parkinsonian tremor are shown in Figure 2. The region of Vc was divided into four quadrants (numbered 1–4) by two bold lines (Fig. 2B). The bold horizontal line was defined by the ACPC line, a radiologic landmark (Lenz et al., 1988a). The bold line perpendicular to the ACPC line was aligned with the most posterior cell with an RF to innocuous somatosensory stimulation. This vertical line was assumed to define the posterior border of Vc. The present data were analyzed according to this coordinate system. Paresthesias were the most common sensations evoked. Thermal (warm or cool) sensations were evoked by stimulation in the area below the ACPC line (Fig. 2, quadrant 2, sites 43 and 44). Thermal sensations were also evoked behind the vertical line, where cells do not have RFs (Fig. 2, quadrant 3, site 46). Pain was evoked by stimulation at one site in the posterior-inferior region (Fig. 2, quadrant 3, site 45). No sensation was evoked by stimulation at three sites (Fig. 2, sites 33, 37, and 39).

Figure 3 shows an example of the results of stimulation and recording in a patient with pain in the lower abdomen and leg after a thoracic cordotomy for treatment of pain from a sciatic nerve injury. The patient had no hyperalgesia to cutaneous stimuli. Thermal sensations were not evoked, but pain sensations were evoked by stimulation in the representation of the painful part of the body, located in the posterior-inferior region (Fig. 3, quadrant 3, sites 31 and 32); nonpainful paraesthesias were the most common response (Lenz et al., 1993a).

Figure 4 shows activity recorded in a patient with pain after a lesion of the central nervous system—a stroke of the inferior parietal, posterior temporal, and anterior occipital cortex. This patient had cutaneous hyperalgesia to cold, warm, and mechanical stimuli applied to the hand and leg. Large numbers of cells with cutaneous receptive fields were recorded (Fig. 4, sites 4–14). Posterior to the representation of cutaneous structures in the core, two cells responded to stimulation of deep structures (Poggio and Mountcastle, 1963; Jones et al., 1982; Kaas et al., 1984; Lenz et al., 1988b). Thermal sensations were not evoked, but pain was evoked by stimulation within the

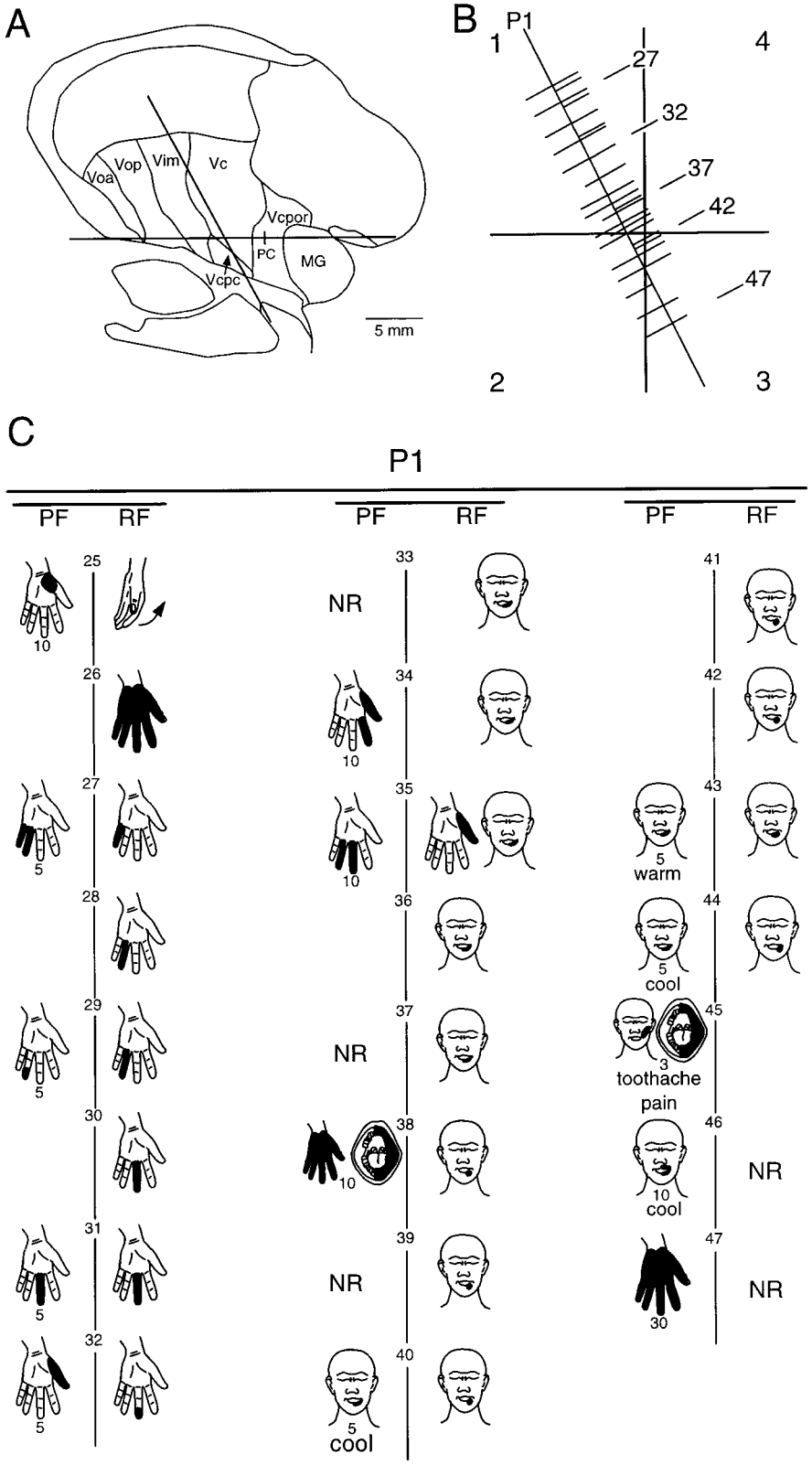

Fig. 2. Map of receptive fields (RF)and projected fields (PF) for the trajectory 16 mm lateral to the midline in a patient with Parkinsonian tremor but no pain or sensory loss. **A:** Position of the trajectory (indicated by the oblique line) relative to the anterior commissure-posterior commissure (ACPC) line and the nuclear boundaries as estimated radiologically (Lenz et al., 1993a). **B:** Location of the cells, stimulation sites, and trajectory S2 relative to the posterior commissure. Stimulation sites are located by ticks to the left of the trajectory. Short ticks to the left of the trajectory indicate that no sensation is evoked by stimulation, and long ticks indicate that a tingling sensation is evoked by stimulation unless listed otherwise. Cellular recordings are located by ticks to the right of the trajectory. Cells with RFs are indicated by long ticks; those without RFs are indicated by short ticks. The bold vertical line is defined by the anterior-posterior location of the last cell with an RF to innocuous somatosensory stimulation, which defined the posterior border of the core of the ventral caudal thalamic nucleus (Vc). The bold horizontal line is the ACPC line. Each site where a cell was recorded, or where a stimulation was carried out, or both is indicated by the same number in B and C. **C:** Illustrations showing the site number, PF, and RF for each site. The threshold (in μA) is indicated below the PF figurines. For other abbreviations, see list (abbreviations and definitions according to Merskey, 1986).

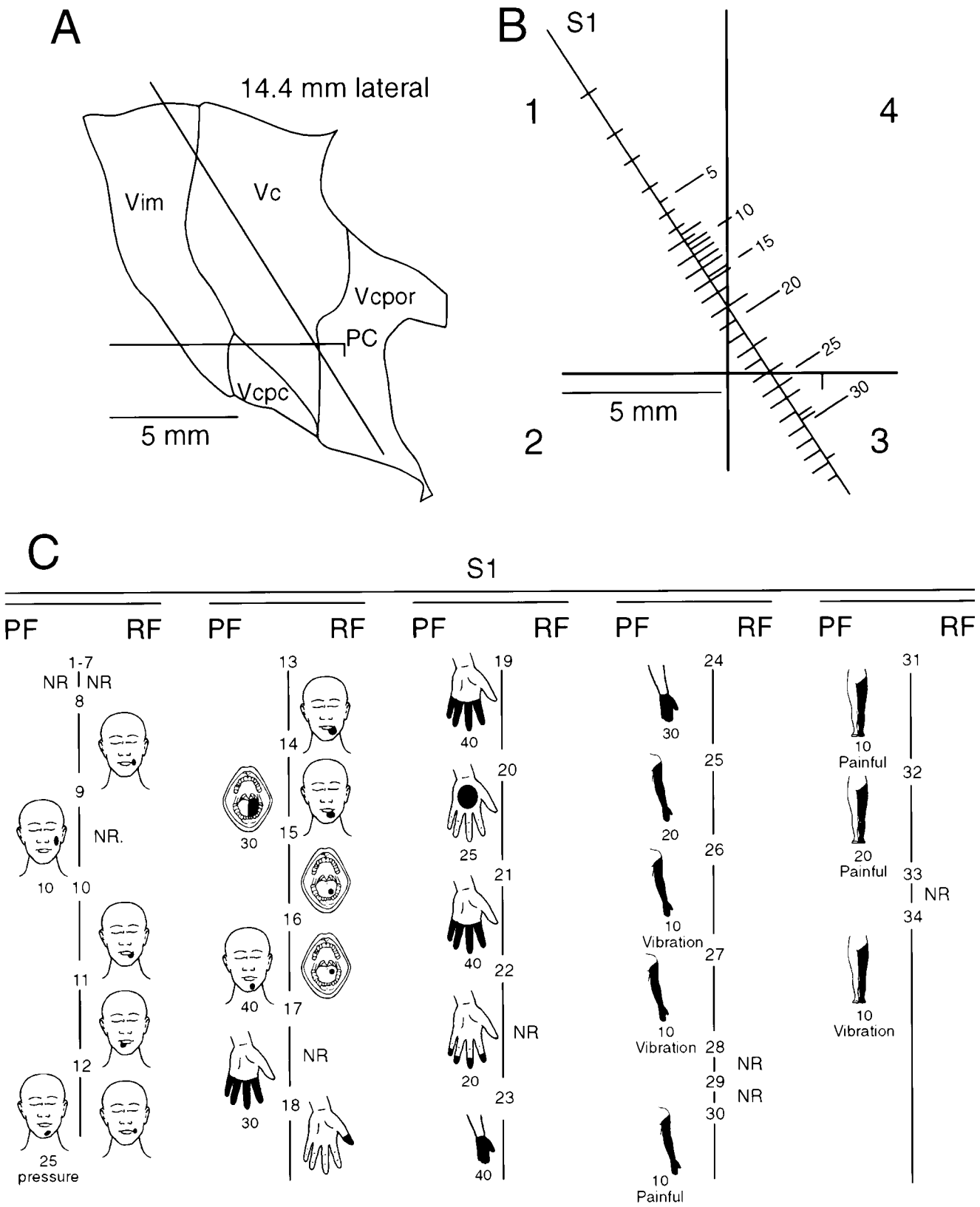

Fig. 3. **A–C:** Map of receptive and projected fields for a patient with pain following a thoracic cordotomy. This patient had pain and hyperalgesia to cold stimuli applied in the lower extremity. For other conventions, see Figure 2. For abbreviations, see list.

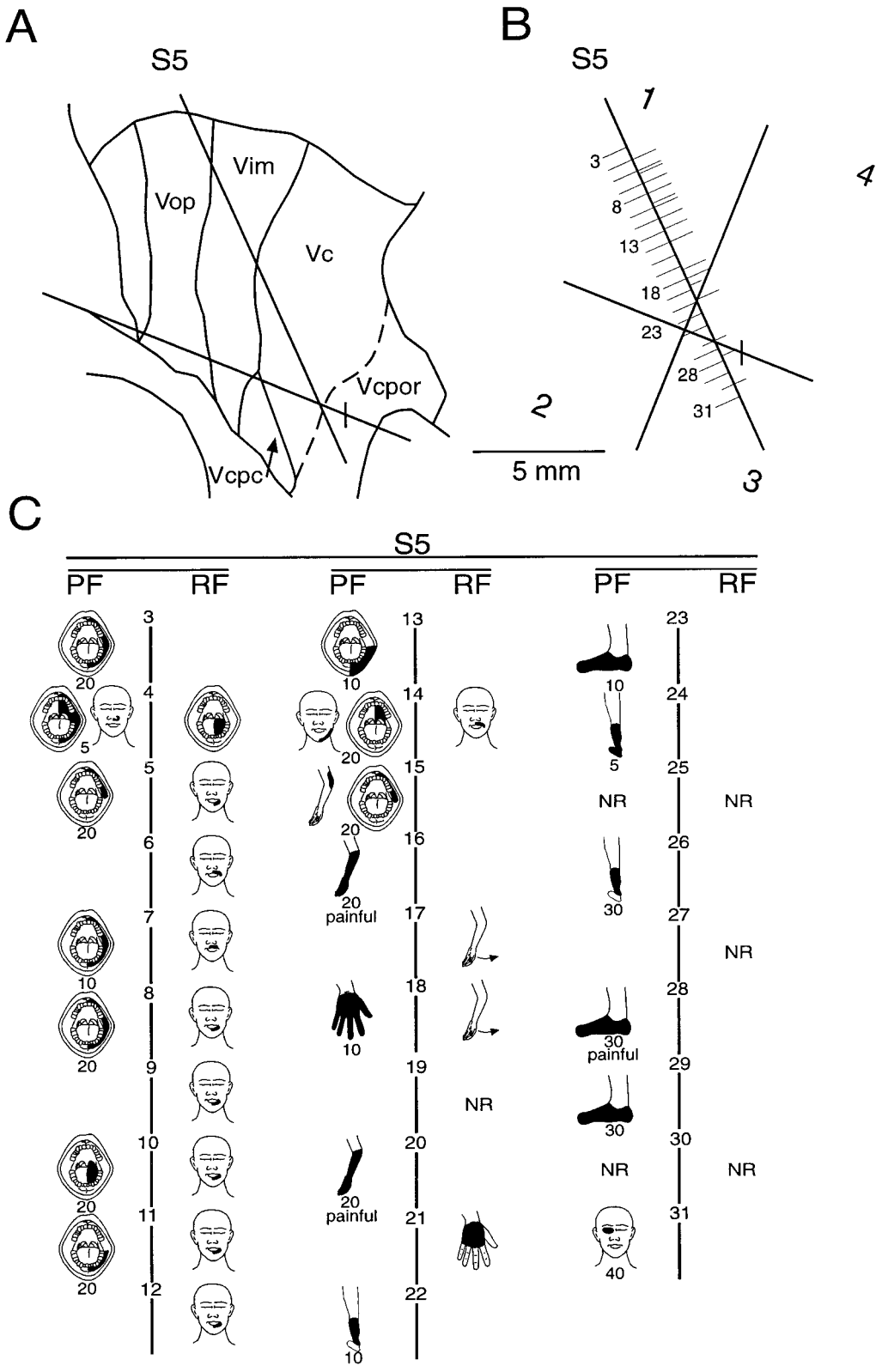

Fig. 4. **A–C:** Map of receptive and projected fields for a patient with pain following a temporoparietooccipital stroke. This patient had pain and hyperalgesia to cold and mechanical stimuli applied to the arm and leg. The bold axes are angled off the horizontal and vertical, because the stereotactic frame was placed at an angle to the ACPC line in this case. For conventions, see legend Figure 2. For abbreviations, see list.

TABLE 1. Proportion of Sites at Which Thermal or Pain Sensations Were Evoked by Stimulation Relative to the Four Quadrants in the Region of the Ventral Caudal Thalamic Nucleus

Location	Anterior to most posterior cell with a receptive field	Posterior to most posterior cell with a RF receptive field
Above the ACPC line[1]	6.8% (9/133)	21.6% (11/51)
Below the ACPC line	23.1% (12/52)	34.0% (36/106)

[1]ACPC, anterior commisure-posterior commisure line.

core region in this patient (Fig. 4, quadrant 1, sites 16 and 20) and in the posterior-inferior region (Fig. 4, quadrant 3, site 28).

The patient's with chronic pain had pain as a result of diverse injuries to the nervous system. Therefore, we tested for differences in the proportions of TMIS-evoked sensations (thermal, pain) among patients with pain by using a test of association in a contingency table in which all expected numbers were small (Maxwell, 1961). The results of this analysis demonstrated that differences in the proportions of different TMIS-evoked sensations between patients were not significant ($P > 0.05$). In addition, differences between classes of patients with chronic pain were not significant (see Table 4). Therefore, all patients with chronic pain were grouped together for the first analysis.

Region of Vc

Table 1 shows the incidence of pain-plus-thermal sites in each of the quadrants. Statistical testing revealed highly significant differences in the proportions of thermal or pain sites in the four quadrants ($P < 0.0001$; χ^2 test). Significant differences were observed between quadrant 1 and each of quadrants 2, 3, and 4 ($P < 0.05$; χ^2 test). Differences between quadrants 2, 3, and 4 were not significant ($P > 0.4$; χ^2 test). The thresholds for paresthesias, thermal, or pain sensations were not significantly different between the four quadrants (one-way analyses of variance [ANOVAs]; degrees of freedom [df] = 3; $P > 0.3$). Therefore, results were analyzed separately for the core region (quadrant 1) and the posterior-inferior area (quadrants 2, 3, and 4).

Figure 5 shows percentages of different types of sensory responses as a function of thalamic region studied. In the region of Vc (i.e., core and posterior-inferior areas combined; Fig. 5A), the proportions of sites where pain was evoked varied significantly according to the control, pain-affected, and pain-unaffected classification ($P < 0.003$; χ^2 test). Post-hoc analysis revealed that pain responses were much more common in pain-affected areas($P < 0.001$; χ^2 test) and pain-unaffected areas ($P < 0.01$; χ^2 test) than in control areas. Proportions of sites where TMIS-evoked sensations were more common in control areas than in pain-affected areas for the following sensations: thermal (warm or cold; $P < 0.0001$; χ^2 test), warm ($P < 0.02$; χ^2 test), and cold ($P < 0.0002$; χ^2 test). The proportion of sites where either pain or thermal responses were evoked did not vary significantly among control, pain-affected, and pain-unaffected areas ($P > 0.1$; χ^2 test). Therefore, compared with control areas, stimulation of pain-affected and pain-unaffected areas evoked thermal sensations less commonly and evoked pain more commonly. The amount of the decrease in frequency of thermal sensations was similar to the increase in the frequency of pain sensations, suggesting a reciprocal relationship between the numbers of sites where pain sensations were evoked and those where thermal sensations were evoked.

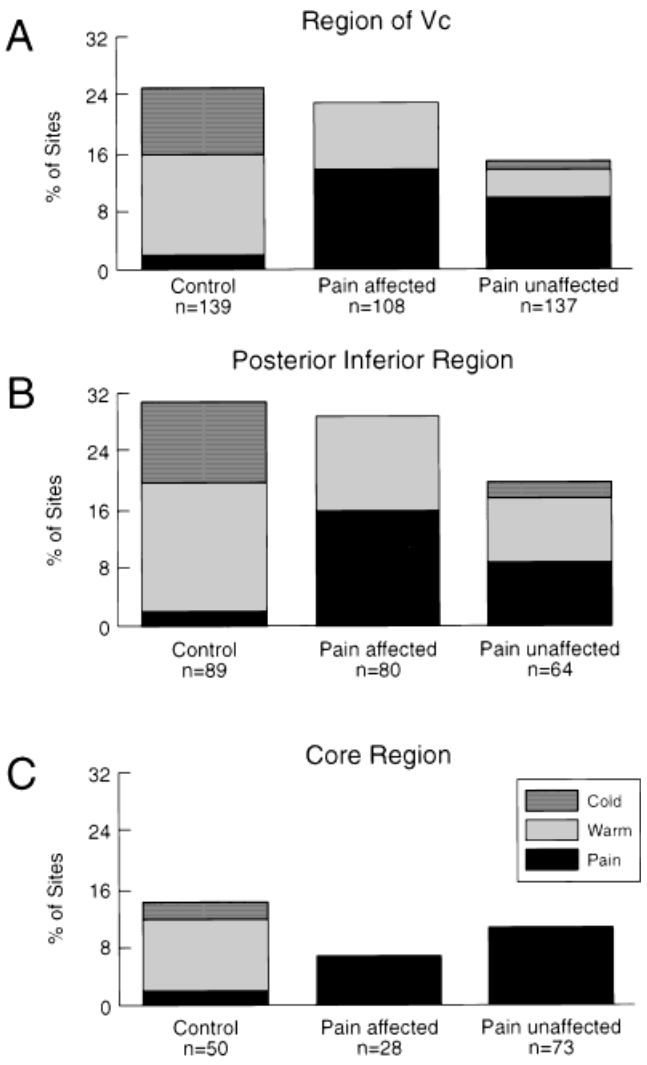

Fig. 5. **A–C:** Percentages of pain, cold, and warm sensations evoked by stimulation in the core (C) and in posterior-inferior areas separately (B) and combined (A). Percentages are shown for movement-disorder patients and for areas of the thalamus representing the part of the body where the patient does (pain affected) or does not (pain unaffected) experience pain.

Posterior-inferior and core regions

The same effect was seen in the results from the posterior-inferior region that are summarized in Figure 5B. The proportion of sites where pain was evoked was significantly different among control, pain-affected, and pain-unaffected areas ($P < 0.01$; Fisher's exact test). Post-hoc testing revealed that the proportion of sites where stimulation evoked pain in control areas (2%) was not significantly different from that in pain-unaffected regions (9%; $P < 0.068$; Fisher's exact test), but the sites were significantly less common in control areas than in pain-affected areas (16%; $P < 0.0019$; Fisher's exact test). Stimulation-evoked cold sensations ($P < 0.001$; Fisher's exact test) were significantly less common in pain-affected and pain-unaffected areas than in control areas, but warm

TABLE 2. Thresholds (μA) for Evoking Sensations as a Function of Thalamic Region and Sensation

Sensation	Pain affected[1]	Pain unaffected	Control
Pain	19.1 ± 2.5 (n = 15)	20.5 ± 3.2 (n = 14)	9.1 ± 3.5 (n = 3)
Warm	17.3 ± 3.7 (n = 10)	9.1 ± 2.4 (n = 6)	12.3 ± 2.3 (n = 21)
Cold	NA (n = 0)	5 (n = 1)	11.3 ± 2.8 (n = 11)
Paresthesias	15.8 ± 1.3 (n = 83)	16.3 ± 1.3 (n = 116)	15.1 ± 0.9 (n = 104)

[1]Values are mean ± SEM. NA, not available.

sensations were not significantly different ($P > 0.25$; χ^2 test). There was no difference in the proportions of stimulation-evoked thermal-plus-pain sensations ($P > 0.25$; χ^2 test) among the three areas. These results suggest a reciprocal relationship in the posterior-inferior region between the frequency of sites where pain was evoked in patients with chronic pain and sites where cool sensations were evoked by TMIS in patients with movement disorders.

Results were similar in the core region, as shown in Figure 5C. Here, sites where pain was evoked tended to be more frequent in pain-affected and pain-unaffected than in control areas ($P > 0.15$; Fisher's exact test). No thermal sensations were found in the pain-affected and pain-unaffected areas. In pain-affected and pain-unaffected areas, TMIS-evoked sensations were reported less frequently than in control areas for thermal sensations (warm and/or cold; $P < 0.01$; Fisher's exact test) and warm sensations ($P < 0.01$; Fisher's exact test) but not cold sensations ($P > 0.25$; Fisher's exact test). The proportion of thermal-plus-pain sensations was not significantly different ($P > 0.30$; Fisher's exact test) among pain-affected, pain-unaffected, and control areas. These results suggest a reciprocal relationship between sites where pain and warm sensations were evoked in the core region.

Thresholds for TMIS-evoked sensations did not vary significantly ($P > 0.05$; one-way ANOVAs following a three-way ANOVA) by thalamic region (core vs. posterior-inferior area), PF area (pain-affected, pain-unaffected, and control areas), and sensation (pain, warm, cold, and paresthesia). Although none of the main effects was significant, the interaction term for region and sensation was significant ($F = 2.46$; $P < 0.05$). Differences between thresholds for evoking pain in the pain-affected category (19.1 + 2.48; n = 15; see Table 2) and those for evoking warmth in the pain-unaffected category (9.1 + 2.38; n = 6) were significant ($P < 0.05$; post-hoc Bonferroni test). Although this result is statistically significant, its physiological significance is unclear.

Central pain

Quantitative sensory testing has demonstrated a deficit in thermal and pain sensibility in all patients with pain after injuries to the central nervous system, i.e., central pain (Beric et al., 1988; Boivie et al., 1989; Andersen et al., 1995). Therefore, TMIS-evoked sensations were analyzed in this subset of patients (Table 3). This analysis revealed that the number of sites where thermal sensations were evoked (pain-affected and pain-unaffected areas combined) was significantly ($P < 0.0005$; χ^2 test) less in patients with central pain than that in patients with movement disorders. The same pattern was seen for cold sensations ($P < 0.005$) but not for warm sensations ($P > 0.2$; χ^2 test). Pain was evoked more frequently ($P < 0.0001$, χ^2) in patients with central pain than in patients with movement disorders, but the number of pain-plus-thermal sites was not significantly different ($P > 0.08$; χ^2 test). Thus, results in the patients with central pain suggest a reciprocal relation between cold and pain sensations.

TABLE 3. Proportions of Sites at Which Different Sensations are Evoked by Stimulation in the Pain-Affected and Pain-Unaffected Regions in Central Pain Patients[1]

Group	Pain % (no.)	Thermal % (no.)	Pain and thermal % (no.)	Warm % (no.)	Cold % (no.)
Control	2 (3/139)	23 (32/139)	25 (35/139)	15 (21/139)	8 (11/139)
Pain affected	23 (16/71)	14 (10/71)	37 (26/71)	14 (10/71)	0 (0/71)
Pain unaffected	8 (6/74)	9 (7/74)	18 (13/74)	8 (6/74)	1 (1/74)

[1]Central pain, pain following a central nervous system injury; thermal, sensation of warm or cold.

TABLE 4. Incidence of Sites and Thresholds for Evoking Different Sensations in Patients With Movement Disorders, Poststroke Central Pain, and Non Poststroke Central Pain

Sensation	Nonpoststroke pain % (no.)	Poststroke pain % (no.)	Movement disorder % (no.)
Paresthesia	84 (145/173)	75 (54/72)	75 (104/139)
Mean ± S.E.M.	15.6 ± 1.1	18.5 ± 3.7	15.1 ± 0.9
Thermal	5 (9/173)	11 (8/72)	23 (32/139)
Mean ± S.E.M.	22.9 ± 6.1	14.5 ± 3.7	11.9 ± 2.5
Pain	11 (19/173)	14 (10/72)	2 (3/139)
Mean ± S.E.M.	16.4 ± 6.1	21.0 ± 3.0	9.1 ± 3.5

TABLE 5. Numbers of Sites at Which Different Sensations are Evoked by Stimulation in the Pain-Affected Area in Patients With and Without Hyperalgesia[1]

Sensation	Hyperalgesia	Nonhyperalgesia
Pain	8	21
Warm	1	15
Cool	1	0

[1]Fisher's exact test ($P > 0.05$).

TMIS-evoked sensations were next examined in the core region of patients with central pain after brain injuries (PSP), because pain may be evoked more commonly in this group (Davis et al., 1996). The proportion of sites in the region of Vc where pain was evoked in patients with PSP (10/72; 14%) tended to be higher than in patients with non-PSP (11%; 19/173; $P > 0.20$; Fisher's exact test). Thus, the present results demonstrate that TMIS-evoked pain tends to be more common in patients with PSP.

Results in patients with hyperalgesia

Pain may be evoked more frequently in patients with chronic pain plus hyperalgesia than in those without hyperalgesia (Gorecki et al., 1989; Tasker and Dostrovsky, 1989). Therefore, numbers of sites where TMIS-evoked pain, warm, and cool sensations in patients with and without hyperalgesia were compared (Table 5). The proportion of sites where pain was evoked, expressed as a fraction of the number of sites where pain, warm, and cold were evoked, tended to be higher (8/10; 80%) in patients with hyperalgesia (Table 5) than in patients without hyperalgesia (21/36; 58%; $P > 0.05$; χ^2 test). In pain-affected areas, pain tended to be evoked more frequently by stimulation ($P < 0.062$; Fisher's exact test) when the PF included the part of the body where the patient experienced hyperalgesia (100%; Table 5) than when it included the part of the body where the patient did not experience hyperalgesia (55%). Thus, there was a consistent tendency to evoke pain

TABLE 6. Numbers of Sites at Which Different Sensations are Evoked by Stimulation in the Part of the Thalamus Representing the Painful Part of the Body Where the Patient Does or Does Not Experience Hyperalgesia[1]

Sensation	Hyperalgesia	Nonhyperalgesia
Pain	6	12
Warm	0	10
Cool	0	0

[1]Fisher's exact test ($P < 0.062$).

by stimulation of thalamic areas representing parts of the body exhibiting hyperalgesia (Table 6).

DISCUSSION

Reorganization of thalamic maps has been reported previously in patients with chronic pain after specific injuries of the nervous system (Lenz et al., 1987, 1994c, 1998). The present report documents the reorganization in sensory modalities evoked by microstimulation in the thalamus of patients with chronic pain after injuries to the nervous system. Compared with movement-disorder patients, patients with chronic neuropathic pain exhibit a greater number of sites where pain is evoked by stimulation. There is a corresponding decrease in the number of sites where thermal (warm and cold) sensations are evoked. These findings suggest that, in patients with neuropathic pain, sites where thermal sensations are evoked normally may have been transformed into sites where pain is evoked by stimulation.

Evidence of pain and thermal processing in the region of Vc

There is ample evidence for nociceptive and thermal processing in the region of Vc. Studies of patients at autopsy following lesions of the spinothalamic tract (STT) show that STT terminals form dense, irregular clusters in the core of Vc (Walker, 1943; Bowsher, 1957; Mehler et al., 1960; Mehler, 1962, 1966). In addition, terminations are observed posterior to Vc in the magnocellular medial geniculate (Mehler, 1962, 1969), limitans, and Vc portae (Mehler, 1966) nuclei and inferior to Vc in parvocellular Vc (Vcpc; Mehler, 1966). Similarly, in monkeys, dense clusters of STT terminations are seen in the ventral posterior nucleus (VP; Boivie, 1979; Berkley, 1980; Mantyh, 1983; Apkarian and Hodge, 1989). Projections are less dense inferior to the ventral posterior lateral nucleus (VPL) in the ventral posterior inferior nucleus (VPI; Apkarian and Hodge, 1989), which corresponds to the human Vcpc (Hirai and Jones, 1989), and posterior to VPL in the posterior nuclear group, including the posterior nucleus (Boivie, 1979; Berkley, 1980; Burton and Craig, 1983; Mantyh, 1983; Ralston and Ralston, 1992); the pulvinar oralis (Apkarian and Hodge, 1989), limitans (Mantyh, 1983; Apkarian and Hodge, 1989), magnocellular medial geniculate (Berkley, 1980), suprageniculate (Berkley, 1980; Mantyh, 1983; Apkarian and Hodge, 1989; Ralston and Ralston, 1992) nuclei; and the ventral medial posterior thalamic nucleus (Vmpo; Craig et al., 1994).

Some cells in the core of Vc have a significant differential response to painful as opposed to nonpainful heat (Lenz et al., 1993b) and mechanical stimuli (Lenz et al., 1994b). Cells in the posterior-inferior region have a significant selective response to noxious heat stimuli (Lenz et al., 1993b). Other cells in the core respond to innocuous mechanical and cool stimuli (Lenz and Dougherty, 1998). These reports extend to humans the results of numerous monkey studies in which cells within VP (Casey, 1966; Kenshalo et al., 1980; Gautron and Guilbaud, 1982; Casey and Morrow, 1983; Hirsch et al., 1983; Chung et al., 1986; Bushnell and Duncan, 1987; Bushnell et al., 1993; Apkarian and Shi, 1994) and posterior and inferior to VP respond to noxious and thermal stimuli in monkeys (Casey, 1966; Hirsch et al., 1983; Apkarian and Shi, 1994; Craig et al., 1994). The location of these cells is consistent with the pattern of STT terminations (Apkarian and Shi, 1994; Craig et al., 1994). Finally, the thermal and pain sensations evoked by stimulation are similar both posterior and inferior to the core (see Table 1; Lenz et al., 1993a; Tasker et al., 1980). Thus, several lines of evidence link the core and the posterior-inferior region to thermal and pain sensation.

Methodologic considerations

Alterations in the physiology of the region of Vc in patients with nervous system injury may result in the region of Vc being smaller in these patients. The region of Vc includes the core of Vc and the *cellular* region posterior and inferior to the core, where stimulation evokes sensations. The core is defined as the area where the majority of cells respond to sensory stimulation (Lenz et al., 1988b). The core in patients with chronic neuropathic pain often has more cells without RFs than in patients with movement disorders (Lenz et al., 1994c, 1998). Therefore, our definition will exclude stimulation sites located in the anterior aspect of the region of Vc, where cells have RFs in patients with movement disorders but do not have RFs in patients with chronic pain as a result of deafferentation (Lenz et al., 1994c).

The decision to combine areas inferior and posterior to the core of Vc into one region (Table 1) is arbitrary but is consistent with anatomy, connectivity, and physiology of this region. Cytochrome oxidase (CO) staining labels terminations of the medial lemniscus and, thus, is stronger in anterior-posterior rods through the core region (rod domain). In posterior VP and posterior-inferior to VP, including VPI and the anterior pulvinar, CO staining is weaker and homogeneous (matrix domain; Rausell and Jones, 1991a,b; Rausell et al., 1992a). These two domains stain for one of two different calcium-binding proteins, parvalbumin in the rod domain and calbindin in the matrix domain (Rausell and Jones, 1991a; Rausell et al., 1992a). The physiology of the region of Vc also suggests that regions posterior and inferior to the core have similar properties (see above).

Vcpc is located below the core and below the ACPC line (Fig. 2A) and corresponds to VPI in monkeys (Hirai and Jones, 1989). Cells in VPI respond to innocuous somatosensory stimuli (Dykes et al., 1981; Kaas et al., 1984; Apkarian and Shi, 1994) and often respond to noxious stimuli (Lenz et al., 1993b; Apkarian and Shi, 1994). Because histologic confirmation of the borders of Vcpc is not an option in the present study, the inferior border of the core of Vc is defined arbitrarily by the ACPC line. This definition appears to be a reasonable approximation, because similar sensations were evoked throughout the posterior-inferior region (Table 1; Dostrovsky et al., 1991; Lenz et al., 1993a).

The present analysis might be explained by a predisposition for patients with chronic pain to describe any sensa-

tion as painful, although this is contrary to prior observations (Lenz et al., 1995a). Furthermore, this explanation cannot account for association of increased numbers of sites where TMIS evoked pain with decreased numbers of sites where TMIS evoked thermal sensations (Fig. 5).

Reciprocal relationship between numbers of sites where pain and thermal sensations are evoked

In patients with chronic neuropathic pain, the increase in the number of sites where pain is evoked corresponds to a decrease in the number of sites where thermal sensations are evoked. Thermal sensations are often evoked by threshold stimulation of the STT (Sweet et al., 1950; Tasker, 1988), whereas pain may be evoked by suprathreshold stimulation of the STT (Price and Mayer, 1975). Because the STT projects to the region of Vc, it is likely that thermal and pain sensations are evoked by stimulation of the STT or of neural elements to which it projects (Apkarian and Shi, 1994) in the region of Vc (Lenz et al., 1993a). The proportion of sites where warm and cold sensations were evoked by stimulation in patients with movement disorders (Fig. 5) was consistent with that previous report. Because thermal sensations are usually accompanied by tingling, the thermal component may not have been identified in previous studies that did not use standardized psychophysical techniques (Levin, 1966; Obrador and Dierssen, 1966; Dierssen et al., 1969; Mazars et al., 1974; Davis et al., 1996). Proportions of sites in the core where pain was evoked (2%) were exactly the same in the present study (Table 3; Fig. 5C, top row) and in previous reports (Lenz et al., 1993a; Davis et al., 1996). The proportion of sites where TMIS evokes pain is increased in patients with chronic pain, particularly those with PSP (Levin, 1966; Obrador and Dierssen, 1966; Dierssen et al., 1969; Mazars et al., 1974; Lenz et al., 1988c; Davis et al., 1996). Therefore, the present results are consistent with many previous reports.

Painful sensations can be evoked by cortical stimulation in patients with chronic pain in a phantom limb (Echols and Colclough, 1947; Erickson et al., 1952; Lewin and Phillips, 1952; Kenshalo and Willis 1991), or in a stump (Erickson et al., 1952), or in patients with PSP (Lewin and Phillips, 1952; Hamby, 1961). These observations were made during stimulation of the representation of the painful part of the body prior to corticectomy for treatment of chronic pain. In contrast, pain is evoked very infrequently by stimulation of cortex in patients without chronic pain (Penfield and Rasmussen, 1955).

Prior evidence for and implications of modality reorganization

The present results suggest that pain is evoked in patients with neuropathic pain by stimulation at sites where thermal sensations would be evoked normally. Therefore, the present data suggest that the STT or elements to which the STT projects signal pain rather than thermal sensations in patients with neuropathic pain. This is consistent with the finding that stimulation of the STT evokes pain in patients with neuropathic pain (Tasker, 1982) but evokes nonpainful thermal sensations in patients who do not have neuropathic pain (Tasker, 1988). Anterolateral cordotomy relieves pain in a much greater proportion of patients with somatic pain than it does in patients with neuropathic pain (Tasker et al., 1980; Sweet et al., 1994). The failure of cordotomy to relieve neuropathic pain might be anticipated from the occurrence of central pain in patients with impaired function of the STT (Cassinari and Pagni, 1969; Beric et al., 1988; Boivie et al., 1989; Andersen et al., 1995). These results suggest that the generator for pain in patients with central pain is the terminus of the STT.

In patients with central pain, damage to the STT is a common finding (Cassinari and Pagni, 1969), and loss of STT function, indicated by impaired thermal and pain sensibility, is a uniform finding (Beric et al., 1988; Boivie et al., 1989; Andersen et al., 1995). In patients with central pain, TMIS-evoked pain is more common than in control areas, whereas TMIS-evoked cold sensations are correspondingly less common. These findings suggest that there has been a reorganization, so that cold modalities are relabeled to signal pain in the thalamus of patients with central pain. This reorganization might occur as a response to STT injury, because dramatic changes in thalamic anatomy can result from interruption of sensory input (Rausell et al., 1992b; Ralston et al., 1996). The relationship in patients with central pain (Table 3) may explain the perception of cold as pain (cold hyperalgesia) that can occur in these patients (Fruhstorfer and Lindblom, 1984; Boivie et al., 1989).

Thalamic plasticity in the organization of inputs and in the image of the body contained in the thalamus

In primates, there are well-documented alterations in thalamic anatomy and physiology after peripheral nerve injury. The distributions of thalamic CO staining and calcium-binding proteins are both altered (Rausell et al., 1992b) in monkeys with a cervical 2-thoracic 4 (C2-T4) dorsal rhizotomy (Sweet, 1981; Levitt, 1985). In the affected arm area of rhizotomized animals, there is a reduction in the density of large cells and of parvalbumin and CO staining, all of which are characteristic of the terminal zone for dorsal column inputs. There is corresponding increase in the calbindin staining in the arm area. The area of Vc occupied by cells with RFs representing the stump is increased dramatically in the Vc of patients with amputations (Lenz et al., 1998). After cervical dorsal rhizotomy, large numbers of cells without RFs are encountered (Lombard et al., 1979; Albe-Fessard and Lombard, 1983) in the forelimb region of the monkey VP. Following adult digit amputation, increased representation of the stump is found, with large RFs that include adjacent digits (Rasmusson, 1996a,b). The thalamic representation of the border of the anesthetic part is increased in monkeys with nerve sections (Garraghty and Kaas, 1991).

Reorganization of cortical activity has also been studied after interruption of peripheral nerves. These studies have shown reorganization of cortical somatotopy over distances of up to 2 mm in macaques (Kaas et al., 1983; Merzenich et al., 1983). Many cells did not have RFs, suggesting that incomplete reactivation occurs in cortex after peripheral nerve section (Rasmusson, 1982; Kaas et al., 1983; Kelahan and Doestch, 1984; Wall and Cusick, 1984). Following a C2-T4 dorsal rhizotomy in macaques (Pons et al., 1991), shifts of 1–2 cm were observed in the map of inputs to cortex. This was an order of magnitude larger than shifts observed in more limited nerve sections (Kaas et al., 1983; Kelahan and Doestch, 1984; Wall and Cusick, 1984).

Similar changes are observed after central nervous system injury. In patients with spinal transection, the numbers of cellular RFs representing the border of the anesthetic part of the body are increased (Lenz et al., 1994c). Following transection of the dorsal columns at the T3–T5 level, activity in simian VP (Pollin and Albe-Fessard, 1979) shows an increase in the percentage of cells with forelimb RFs. Many cells have large RFs and respond to high-threshold inputs, consistent with inputs from the STT. Therefore, loss of input due to peripheral or central nervous system injury leads to significant reorganization of the thalamic representation of inputs from different parts of the body (RF map).

Patients with nervous system injury show changes in the image of the body contained in the thalamus, as revealed by somatotopic PF maps (Lenz et al., 1994c, 1998). In patients with spinal transections, the incidence of mismatches between neuronal RFs and TMIS-evoked PFs at the same sites is much higher than in patients with movement disorders (Lenz et al., 1994c). These mismatches occur because sensations in the anesthetic part are evoked by stimulation at sites where cellular RFs now represent parts of the body that are proximal to the anesthetic part. These results suggest that the image of the body in the thalamus (PF map) reorganizes less in response to nervous system injury than the representation of inputs to the thalamus (RF maps). Although the image of the body contained in the thalamus is relatively constant in the face of altered input, the present results show that dramatic changes can occur in the modality organization of this image. This plasticity of modality organization may contribute to the development of chronic pain.

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LITERATURE CITED

Albe-Fessard, D.G. and M.C. Lombard (1983) Use of an animal model to evaluate the origin of and protection against deafferentation pain. Adv. Pain Res. Ther. *5:*691–700.

Andersen, P., K. Vestergaard, M. Ingeman-Nielsen, and T.S. Jensen (1995) Incidence of post-stroke central pain. Pain *61:*187–193.

Apkarian, A.V. and C.J. Hodge (1989) Primate spinothalamic pathways: III. Thalamic terminations of the dorsolateral and ventral spinothalamic pathways. J. Comp. Neurol. *288:*493–511.

Apkarian, A.V. and T. Shi (1994) Squirrel monkey lateral thalamus. I. Somatic nociresponsive neurons and their relation to spinothalamic terminals. J. Neurosci. *14:*6779–6795.

Beric, A., M.R. Dimitrijevic, and U. Lindblom (1988) Central dysesthesia syndrome in spinal cord injury patients. Pain *34:*109–116.

Berkley, K.J. (1980) Spatial relationships between the terminations of somatic sensory and motor pathways in the rostral brainstem of cats and monkeys. I. Ascending somatic sensory inputs to lateral diencephalon. J. Comp. Neurol. *193:*283–317.

Boivie, J. (1979) An anatomic reinvestigation of the termination of the spinothalamic tract in the monkey. J. Comp. Neurol. *168:*343–370.

Boivie, J., G. Leijon, and I. Johansson (1989) Central post-stroke pain—A study of the mechanisms through analyses of the sensory abnormalities. Pain *37:*173–185.

Bowsher, D. (1957) Termination of the central pain pathway in man: The conscious appreciation of pain. Brain *80:*606–620.

Burton, H. and A.D. Craig, Jr. (1983) Spinothalamic projections in cat, raccoon and monkey: A study based on anterograde transport of horseradish peroxidase. In G.R.A.a.S.R. Macchi (ed): Somatosensory Integration in the Thalamus. Amsterdam: Elsevier, pp. 17–41.

Bushnell, M.C. and G.H. Duncan (1987) Mechanical response properties of ventroposterior medial thalamic neurons in the alert monkey. Exp. Brain Res. *67:*603–614.

Bushnell, M.C., G.H. Duncan, and N. Tremblay (1993) Thalamic VPM nucleus in the behaving monkey. I. Multimodal and discriminative properties of thermosensitive neurons. J. Neurophysiol. *69:*739–752.

Casey, K.L. (1966) Unit analysis of nociceptive mechanisms in the thalamus of the awake squirrel monkey. J. Neurophysiol. *29:*727–750.

Casey, K.L. and T.J. Morrow (1983) Ventral posterior thalamic neurons differentially responsive to noxious stimulation of the awake monkey. Science *221:*675–677.

Cassinari, V. and C.A. Pagni (1969) Central Pain. A Neurosurgical Survey. Cambridge, MA: Harvard University Press.

Chung, J.M., K.H. Lee, D.J. Surmeier, L.S. Sorkin, I. Kim, and W.D. Willis (1986) Response characteristics of neurons in the ventral posterior lateral nucleus of the monkey thalamus. J. Neurophysiol. *56:*370–390.

Craig, A.D., M.C. Bushnell, E.T. Zhang, and A. Blomqvist (1994) A specific thalamic nucleus for pain and temperature sensation in macaques and humans. Nature *372:*770–773.

Davis, K.D., Z.H.T. Kiss, R.R. Tasker, and J.O. Dostrovsky (1996) Thalamic stimulation-evoked sensations in chronic pain patients and nonpain (movement disorder) patients. J. Neurophysiol. *75:*1026–1037.

Dierssen, G., B. Odoriz, and C. Hernando (1969) Sensory and motor responses to stimulation of the posterior cingulate cortex in man. J. Neurosurg. *31:*435–440.

Dostrovsky, J.O., F.E.B. Wells, and R.R. Tasker (1991) Pain evoked by stimulation in human thalamus. In Y. Sjigenaga (ed): International Symposium on Processing Nociceptive Information. Amsterdam: Elsevier.

Dykes, R.W., M. Sur, M.M. Merzenich, J.H. Kaas, and R.J. Nelson (1981) Regional segregation of neurons responding to quickly adapting, slowly adapting, deep and pacinian receptors within thalamic ventroposterior lateral and ventroposterior inferior nuclei in the squirrel monkey. Neuroscience *6:*1687–1692.

Echols, D.H. and J.A. Colclough (1947) Abolition of painful phantom foot by resection of the sensory cortex. JAMA *134:*1476–1477.

Erickson, T.C., W.J. Bleckwenn, and C.N. Woolsey (1952) Observations on the post central gyrus in relation to pain. Trans. Am. Neurol. Assoc. 57–59.

Fruhstorfer, H. and U. Lindblom (1984) Sensibility abnormalities in neuralgic patients studied by thermal and tactile pulse stimulation. In C. von Euler (ed): Somatosensory Mechanisms. London: MacMillian, pp. 353–361.

Garraghty, P.E. and J.H. Kaas (1991) Functional reorganization in adult monkey thalamus after a peripheral nerve injury. Neuroreport *2:*747–750.

Gautron, M. and G. Guilbaud (1982) Somatic responses of ventrobasal thalamic neurones in polyarthritic rats. Brain Res. *237:*459–471.

Gorecki, J., T. Hirayama, J.O. Dostrovsky, R.R. Tasker, and F.A. Lenz (1989) Thalamic stimulation and recording in patients with deafferentation and central pain. Stereo. Funct. Neurosurg. *52:*219–226.

Gracely, R.H., R. Dubner, P. McGrath, and M. Heft (1978) New methods of pain measurement and their application to pain control. Int. Dental. J. *28:*52–65.

Hamby, W.B. (1961) Reversible central pain. Arch. Neurol. *5:*582–586.

Hawrylyshyn, P., I.H. Rowe, R.R. Tasker, and L.W. Organ (1976) A computer system for stereotaxic neurosurgery. Comput. Biol. Med. *6:*87–97.

Hirai, T. and E.G. Jones (1989) A new parcellation of the human thalamus on the basis of histochemical staining. Brain Res. Rev. *14:*1–34.

Hirsch, J.C., A. Fourment, and M.E. Marc (1983) Sleep-related variations of membrane potential in the lateral geniculate body relay neurons of the cat. Brain Res. *259:*308–312.

Jones, E.G., D.P. Friedman, and S.H.C. Hendry (1982) Thalamic basis of place and modality-specific columns in monkey somatosensory cortex: A correlative anatomical and physiological study. J. Neurophysiol. *48:*545–568.

Kaas, J.H., M.M. Merzenich, and H.P. Killackey (1983) The reorganization of somatosensory cortex following peripheral nerve damage in adult and developing animals. Annu. Rev. Neurosci. *6:*325–356.

Kaas, J.H., R.J. Nelson, M. Sur, R.W. Dykes, and M.M. Merzenich (1984) The somatotopic organization of the ventroposterior thalamus of the squirrel monkey, *Saimiri sciureus*. J. Comp. Neurol. *226:*111–140.

Kelahan, A.M. and G.S. Doestch (1984) Time dependent changes in the functional organization of somatosensory cerebral cortex following digit amputation in adult raccoons. Somatosen. Res. *2:*49–81.

Kenshalo, D.R., Jr. and W.D. Willis, Jr. (1991) The role of the cerebral cortex in pain sensation. In A. Peters and E.G. Jones (eds): Cerebral Cortex, Vol. 9: Normal and Altered States of Function. New York: Plenum Press, pp. 153–212.

Kenshalo, D.R., G.J. Giesler, R.B. Leonard, and W.D. Willis (1980) Responses of neurons in primate ventral posterior lateral nucleus to noxious stimuli. J. Neurophysiol. *43:*1594–1614.

Lenz, F.A. and P.M. Dougherty (1998) Cells in the human principal thalamic sensory nucleus (ventralis caudalis—Vc) respond to innocuous mechanical and cool stimuli. J. Neurophysiol. *79:*2227–2230.

Lenz, F.A., R.R. Tasker, J.O. Dostrovsky, H.C. Kwan, J. Gorecki, T. Hirayama, and J.T. Murphy (1987) Abnormal single-unit activity recorded in the somatosensory thalamus of a quadriplegic patient with central pain. Pain *31:*225–236.

Lenz, F.A., J.O. Dostrovsky, H.C. Kwan, R.R. Tasker, K. Yamashiro, and J.T. Murphy (1988a) Methods for microstimulation and recording of single neurons and evoked potentials in the human central nervous system. J. Neurosurg. *68:*630–634.

Lenz, F.A., J.O. Dostrovsky, R.R. Tasker, K. Yamashiro, H.C. Kwan, and J.T. Murphy (1988b) Single-unit analysis of the human ventral thalamic nuclear group: Somatosensory responses. J. Neurophysiol. *59:*299–316.

Lenz, F.A., R.R. Tasker, J.O. Dostrovsky, H.C. Kwan, J. Gorecki, T. Hirayama, and J.T. Murphy (1988c) Abnormal single-unit activity and responses to stimulation in the presumed ventrocaudal nucleus of patients with central pain. Pain Res. Clin. Manag. *3:*157–164.

Lenz, F.A., H.C. Kwan, J.O. Dostrovsky, and R.R. Tasker (1989) Characteristics of the bursting pattern of action potentials that occur in the thalamus of patients with central pain. Brain Res. *496:*357–360.

Lenz, F.A., M. Seike, Y.C. Lin, F.H. Baker, R.T. Richardson, and R.H. Gracely (1993a) Thermal and pain sensations evoked by microstimulation in the area of the human ventrocaudal nucleus (Vc). J. Neurophysiol. *70:*200–212.

Lenz, F.A., M. Seike, Y.C. Lin, F.H. Baker, L.H. Rowland, R.H. Gracely, and R.T. Richardson (1993b) Neurons in the area of human thalamic nucleus ventralis caudalis respond to painful heat stimuli. Brain Res. *623:*235–240.

Lenz, F.A., R.H. Gracely, E.J. Hope, F.H. Baker, L.H. Rowland, P.M. Dougherty, and R.T. Richardson (1994a) The sensation of angina can be evoked by stimulation of the human thalamus. Pain *59:*119–125.

Lenz, F.A., R.H. Gracely, L.H. Rowland, and P.M. Dougherty (1994b) A population of cells in the human principal sensory nucleus respond to painful mechanical stimuli. Neurosci. Lett. *180:*46–50.

Lenz, F.A., H.C. Kwan, R. Martin, R. Tasker, R.T. Richardson, and J.O. Dostrovsky (1994c) Characteristics of somatotopic organization and spontaneous neuronal activity in the region of the thalamic principal sensory nucleus in patients with spinal cord transection. J. Neurophysiol. *72:*1570–1587.

Lenz, F.A., R.H. Gracely, A.J. Romanoski, E.J. Hope, L.H. Rowland, and P.M. Dougherty (1995a) Stimulation in the human somatosensory thalamus can reproduce both the affective and sensory aspects of previously experienced pain. Nature Med. *1:*910–913.

Lenz, F.A., S.L. Normand, H.C. Kwan, D. Andrews, L.H. Rowland, M.W. Jones, M. Seike, Y.C. Lin, R.R. Tasker, J.O. Dostrovsky, and Y.E. Lenz (1995b) Statistical prediction of the optimal lesion site for thalamotomy in Parkinsonian tremor. Movement Dis. *10:*318–328.

Lenz, F.A., R. Gracely, A.T. Zirh, A.J. Romanoski, and P.M. Dougherty (1997) The sensory-limbic model of pain memory: Connections from thalamus to the limbic system mediate the learned component of the affective dimension of pain. Pain Focus *6:*22–31.

Lenz, F.A., I.M. Garonzik, T.A. Zirh, and P.M. Dougherty (1998) Characteristics of neuronal activity in the region of the thalamic nucleus Vc in patients with amputations. Neuroscience (in press).

Levin, G. (1966) Electrical stimulation of the globus pallidus and thalamus. J. Neurosurg. *24:*415

Levitt, M. (1985) Dysesthesias and self-mutilation in humans and subhumans: A review of clinical and experimental studies. Brain Res. Rev. *10:*247–290.

Lewin, W. and C.G. Phillips (1952) Observations on partial removal of the post-central gyrus for pain. J. Neurol. Neurosurg. Psychiatr. *15:*143–147.

Lombard, M.C., B.S. Nashold, and T. Pelissier (1979) Thalamic recordings in rats with hyperalgesia. Adv. Pain Res. Ther. *3:*767–772.

Mantyh, P.W. (1983) The spinothalamic tract in primate: A re-examination using wheatgerm agglutinin conjugated with horseradish peroxidase. Neuroscience *9:*847–862.

Maxwell, A.E. (1961) Analyzing Qualitative Data. New York: John Wiley and Sons.

Mazars, G., L. Merienne, and C. Cioloca (1974) Traitement de certains types de douleurs par des stimulateurs thalamiques implantables. Neurochirurgie *20:*117–124.

Mehler, W.R. (1962) The anatomy of the so-called "pain tract" in man: An analysis of the course and distribution of the ascending fibers of the fasciculus anterolateralis. In J.D. French and R.W. Porter (eds): Basic Research in Paraplegia. Springfield: Thomas, pp. 26–55.

Mehler, W.R. (1966) The posterior thalamic region in man. Confin. Neurol. *27:*18–29.

Mehler, W.R. (1969) Some neurological species differences—A posteriori. Ann. N.Y. Acad. Sci. *167:*424–468.

Mehler, W.R., M.E. Feferman, and W.H.J. Nauta (1960) Ascending axon degeneration following anterolateral cordotomy. An experimental study in the monkey. Brain *83:*718–750.

Merskey, H. (1986) Classification of chronic pain. Pain S1–S220.

Merzenich, M.M., J.H. Kaas, J.T. Wall, R.J. Nelson, M. Sur, and D. Felleman (1983) Topographic reorganization of somatosensory cortical areas 3b and 1 in adult monkeys following restricted deafferentation. J. Neurosci. *10:*639–665.

Obrador, S. and G. Dierssen (1966) Sensory responses to subcortical stimulation and management of pain disorders by stereotactic methods. Confin. Neurol. *27:*45–52.

Penfield, W. and T. Rasmussen (1955) The Cerebral Cortex of Man. New York: Macmillan.

Poggio, G.F. and V.B. Mountcastle (1963) The functional properties of ventrobasal thalamic neurons studied in ananesthetized monkeys. J. Neurophysiol. *26:*775–806.

Pollin, B. and D.G. Albe-Fessard (1979) Organization of somatic thalamus in monkeys with and without section of dorsal spinal tracts. Brain Res. *173:*431–449.

Pons, T.P., P.E. Garraghty, A.K. Ommaya, J.H. Kaas, E. Taub, and M. Mishkin (1991) Massive cortical reorganization after sensory deafferentation in adult macaques. Science *252:*1857–1860.

Price, D.D. and D.J. Mayer (1975) Neurophysiological characterization of the anterolateral quadrant neurons subserving pain in *M. mulatta*. Pain *1:*59–72.

Ralston, H.J. and D.D. Ralston (1992) The primate dorsal spinothalamic tract: Evidence for a specific termination in the posterior nuclei [Po/SG] of the thalamus. Pain *48:*107–118.

Ralston, H.J., P.T. Ohara, X.W. Meng, J. Wells, and D.D. Ralston (1996) Transneuronal changes in the inhibitory circuitry of the macaque somatosensory thalamus following lesions of the dorsal column nuclei. J. Comp. Neurol. *371:*325–335.

Rasmusson, D.D. (1982) Reorganization of raccoon somatosensory cortex following removal of the fifth digit. J. Comp. Neurol. *205:*313–326.

Rasmusson, D. (1996a) Changes in the organization of ventroposterior lateral thalamic nucleus after digit removal in the adult raccoon. J. Comp. Neurol. *364:*92–103.

Rasmusson, D.D. (1996b) Changes in the response properties of neurons in the ventroposterior lateral thalamic nucleus of the raccoon after peripheral deafferentation. J. Neurophysiol. *75:*2441–2450.

Rausell, E. and E.G. Jones (1991a) Chemically distinct compartments of the thalamic VPM nucleus in monkeys relay principal and spinal trigeminal pathways to different layers of the somatosensory cortex. J. Neurosci. *11:*226–237.

Rausell, E. and E.G. Jones (1991b) Histochemical and immunocytochemical compartments of the thalamic VPM nucleus in monkeys and their relationship to the representational map. J. Neurosci. *11:*210–225.

Rausell, E., C.S. Bae, A. Vinuela, G.W. Huntley, and E.G. Jones (1992a) Calbindin and parvalbumin cells in monkey VPL thalamic nucleus: Distribution, laminar cortical projections, and relations to spinothalamic terminations. J. Neurosci. *12:*4088–4111.

Rausell, E., C.G. Cusick, E. Taub, and E.G. Jones (1992b) Chronic deafferentation in monkeys differentially affects nociceptive and nonnociceptive pathway distinguished by specific calcium-binding proteins and down-regulates gamma-aminobutyric acid type A receptors at thalamic levels. Proc. Natl. Acad. Sci. USA *89:*2571–2575.

Schaltenbrand, G. and P. Bailey (1959) Introduction to Stereotaxis With an Atlas of the Human Brain. Stuttgart: Thieme.

Sweet, W.H. (1981) Animal models of chronic pain: Their possible validation from human experience with posterior rhizotomy and congenital analgesia. Pain *10:*275–295.

Sweet, W.H., J.C. White, B. Selverstone, and R. Nilges (1950) Sensory responses from anterior roots and from the surface and interior of the spinal cord in man. Trans. Am. Neurol. Assoc. *75:*165–169.

Sweet, W.H., C.E. Poletti, and G.M. Gybels (1994) Operations in the brainstem and spinal canal with an appendix on the relationship of open and percutaneous cordotomy. In P.D. Wall and R. Melzack (eds): Textbook of Pain. New York: Churchill Livingston, pp. 1113–1136.

Tasker, R.R. (1982) Identification of pain processing systems by electrical stimulation of the brain. Hum. Neurobiol. *1:*261–272.

Tasker, R.R. (1988) Percutaneous cordotomy: The lateral high cervical technique. In H.H. Schmidek and W.H. Sweet (eds): Operative Neurosurgical Techniques Indications, Methods, and Results. Philadelphia: W.B. Saunders, pp. 1191–1205.

Tasker, R.R. and J.O. Dostrovsky (1989) Deafferentation and central pain. In P.D. Wall and R. Melzack (eds): Textbook of Pain. Edinburgh: Churchill Livingstone, pp. 154–180.

Tasker, R.R., L.W. Organ, and P. Hawrylyshyn (1980) Deafferentation and causalgia. In J.J. Bonica (ed): Pain. New York: Raven Press, pp. 305–329.

Tasker, R.R., L.W. Organ, and P. Hawrylyshyn (1982) The Thalamus and Midbrain in Man: A Physiologic Atlas Using Electrical Stimulation. Springfield, IL: Thomas.

Walker, A.E. (1943) Central representation of pain. Res. Publ. Assoc. Res. Nerv. Ment. Dis. *23:*63–85.

Wall, J.T. and C.G. Cusick (1984) Cutaneous responsiveness in primary somatosensory (S-1) hindpaw cortex before and after partial hindpaw deafferentation in adult rats. J. Neurosci. *4:*1499–1515.

Zirh, A.T., F.A. Lenz, S.G. Reich, and P.M. Dougherty (1997) Patterns of bursting occurring in thalamic cells during Parkinsonian tremor. Neuroscience *83:*107–121.